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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,016	03/05/2001	Dean K. Pettit	3253	5188

500 7590 05/15/2003

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EXAMINER
SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO

EXAMINER	

ART UNIT	PAPER NUMBER
	11

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-15 is/are pending in the application.
Of the above, claim(s) 14,15 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-13 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-15 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5, 6
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40

Part III: Detailed Office Action

Claims 1-15 are pending and under consideration.

Restriction Requirement:

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-13, drawn to compositions of GM-CSF and methods of using such to treat inflammatory bowel disease, classified in class 424, subclass 198.1.

II. Claims 14 and 15, drawn to treatment of ulcers, classified in class 424, subclass 198.1.

The inventions are distinct, each from the other because:

Although the two inventions share classification based upon the active agent being used, they are nonetheless separate and distinct, and present an undue search burden. The two different methods of use of Invention I and Invention II, although using the same active agent, require non-coextensive searches of the causes and etiology of the conditions being treated, and the prior art on using GM-CSF for the particular condition being treated. The methods of treating IBD are grouped with the produce claims, as the use of GM-CSF for treatment of IBD is old and well known in the art, and does not present a burdensome requirement for search as compared to the composition alone.

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product may be used to treat materially different conditions, or in *in vitro* assays.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Carol Roth on 5/12/03 a provisional election was made

with traverse to prosecute the invention of group I, claims 1-13. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Affirmation of this election must be made by applicant in replying to this Office action. Claims 14-15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The title should convey that EDTA is the stabilizing agent of the invention.

Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 8 is objected to as the step of lyophilizing as recited in claim 8 would not produce a stabilized aqueous solution as recited in claim 5.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is an incomplete method claim, as it does not require any significant amount of GM-CSF. Amendment of the claim to recite, prior to the word "aqueous", –a therapeutically effective amount of– would be remedial. Claims 10 and 14 are similarly indefinite, and the remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, cited by applicants in paper number 5, in view of Chalmers, Manufacturing Chemist & Aerosol News (March 1978, cited by applicants) , and U.S. Patent Number 5,217,954 (Foster et al.), and in the case of claims 4-8, further in view of U.S. Patent Number 5,545,536 (Kaushansky et al.).

The Leukine® patient insert teaches that sargramostim is provided in liquid form at a concentration of 500 mcg/mL (micrograms per milliliter), with 1.1% benzyl alcohol, 40 mg/mL

mannitol, 10 mg/mL sucrose, and 1.2 mg/mL tromethamine (third paragraph of insert). At the bottom of the first column of the third page, and again on the fifth page, there are warnings that preparations containing benzyl alcohol, including both LEUKINE® liquid and lyophilized LEUKINE® reconstituted for injection, should not be used in neonates. The LEUKINE® (sargramostim) insert differs from the claims in that it does not teach inclusion of EDTA, nor the inclusion of TRIS-HCL.

Chalmers teaches the use of EDTA as a chelating agent in foods, toiletries and medicines. He states that "The EDTA range of chelating agents is designed to enable as many different kinds of metals as possible to be controlled or de-ionised as a complex molecule in aqueous solution (page 79). At page 80, he teaches that although EDTA has no germicidal action per se, it will inhibit the growth of certain bacteria by rendering unavailable trace metals required for growth.

Foster et a. teach the use of EDTA as a chelating agent for the stabilization of bFGF, another cytokine. At column 1, they state that the EDTA "stabilizes this protein against oxidation of its free cysteine residues or metal-induced aggregation, thereby preserving the homogeneity of the purified product."

The use of TRIS as a buffering agent in protein and pharmaceutical preparations is notoriously old and well known in the art. For example, Kaushansky et al. teach the use of TRIS buffers in the isolation of GM-CSF, see for example column 17.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to have substituted EDTA for benzyl alcohol in the preparations of sargramostim disclosed in the LEUKINE® insert. One of ordinary skill in the art would have been motivated to make the substitution in order to produce a stable composition that could be administered to neonates, as the insert specifically warns against administering benzyl alcohol to neonates. The specific concentration of EDTA to be added would be easily determinable, and is considered well within the purview of routine experimentation by the ordinary pharmacologist. It further would have been obvious to use TRIS as a buffering agent, as it is notoriously old and well known in the art as such, for example see Kaushansky. Accordingly, the invention, taken as a whole, is *prima face* obvious

over the prior art.

The Examiner notes the results disclosed at page 13 of the specification. The results therein are not considered to be "unexpected", as the person of ordinary skill in the art reading the above-cited references would have expected GM-CSF stored in the presence of EDTA to more stable than that without. It would appear that the results therein merely compare the presence to the absence of EDTA, and do not compare the preparations containing EDTA to comparable prior-art preparations lacking EDTA.

Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, cited by applicants in paper number 5, in view of Chalmers, Manufacturing Chemist & Aerosol News (March 1978, cited by applicants) , and U.S. Patent Number 5,217,954 (Foster et al.), as cited in the rejection of claims 1-9 above, and further in view of U.S. Patent Number 6,500,418 B1 (Dieckgraefe et al.)

Claims 10-13 are drawn to methods of treating IBD, including Crohn's disease, using the composition of claim 1. The references cited in the rejection of claims 1-9 do not specifically disclose treatment of IBD/Crohn's disease with GM-CSF. Dieckgraefe et al. disclose and claim treatment of Crohn's disease with GM-CSF, see claims 1 and 21, especially. It therefore would have been obvious to the person of ordinary skill in the art to substitute the composition of claim 1 in the method of Dieckgraefe et al. to attain the known and expected benefits of treating Crohn's disease with GM-CSF, as disclosed by Dieckgraefe et al. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Advisory Information:

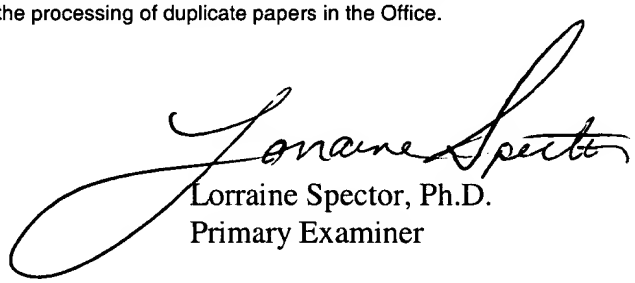
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 5:00 A.M. to 9:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, can be reached at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Examiner Spector via telephone number 703-746-5228. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)), NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.



Lorraine Spector, Ph.D.
Primary Examiner